ISIS-4847 PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:

Muthiah Manoharan

Serial No.: Not Assigned Yet **Group Art Unit: Not Assigned Yet**

Filed: Herewith **Examiner: Not Assigned Yet**

For: **CARBOHYDRATE OR 2'-MODIFIED OLIGONUCLEOTIDES HAVING ALTERNATING INTERNUCLEOSIDE LINKAGES**

EXPRESS MAIL LABEL NO: EL 568090780 US
DATE OF DEPOSIT: September 27, 2001

Assistant Commissioner
for Patents
Washington, D.C. 20231

Preliminary Amendment

Prior to the examination of the above referenced patent application, Applicants respectfully request that the following amendments be entered, without prejudice:

In the specification:

Please replace the section on page 1 having the section heading **CROSS REFERENCE TO RELATED APPLICATIONS** with the following section.

This application is a continuation of U.S. Ser. No. 09/349,007, filed July 7, 1999, which in turn is a continuation-in-part of U.S. Ser. No. 09/115,025, filed July 14, 1998, the disclosures of each of which are incorporated herein by reference in their entireties.

Please replace Table I on page 50 with the replacement Table I as follows.

Table I

Oligonucleotides containing Staggered PS/PO linkages

Oligo #	ISIS #	Sequence (5'-3')[1]	Backbone	Chemistry	Target
1	18268 staggered oligomer	5'-$\mathbf{T_S C^m{}_O T_S G_O A_S G_O T_S A_O G_S C^m{}_O A_S G_O A_S G_O G_S A_O G_S C^m{}_O T_S C}$-3' SEQ ID NO: 1	P=S/P=O	2'-*O*-MOE	*Human ICAM -1*
2	22592 staggered gapmer	5'-$\mathbf{A_S T_O G_S C^m{}_O A_S T_O}$ $T_S C_S{}^m T_S G_S C_S{}^m C_S{}^m C_S{}^m C^m{}_O$ $\mathbf{C^m{}_S A_O A_S G_O G_S A}$-3' SEQ ID NO: 2	P=S/P=O	2'-*O*-MOE & 2'-H	*mouse C-raf*
3	25303 staggered hemimer	5'-$G_S C^m{}_S C^m{}_S C^m{}_S A_S A_S G_S C^m{}_S T_S G_S G_S C^m{}_O$ $\mathbf{A_S T_O C^m{}_S C^m{}_O G_S T_O C^m{}_S A}$-3' SEQ ID NO: 3	P=S/P=O	2'-*O*-MOE & 2'-H	*Human ICAM-1*

[1] All nucleosides in bold are 2'-*O* -MOE (2'-O-CH_2-CH_2-O-CH_3)

Please replace Table III on page 51 with the replacement Table III as follows.

Table III
Tm Values of Human ICAM-1 Antisense Oligonucleotide
ISIS 3067 and Analogs Against RNA Target

5'-TCT GAG TAG CAG AGG AGC TC-3' (SEQ ID NO:4)		
Oligonucleotide	**Modifications**	**Tm**
ISIS 3067 (SEQ ID NO: 5)	**P=S, 2'-deoxy DNA**	**50.1**
ISIS 11910 (SEQ ID NO: 4)	**P=O, 2'-deoxy DNA**	**58.4**
ISIS 11159 (SEQ ID NO: 6)	**P=S, 2'-MOE**	**79.2**
ISIS 11158 (SEQ ID NO: 7)	**P=O, 2'-MOE**	**86.6**
ISIS 18268 (SEQ ID NO: 8)	**P=O/P=S, STAGGERED 2'-MOE**	**84.0**

Please replace Table IV on page 53 with the replacement Table IV as follows.

Table IV

Controlling P=S Linkages: ICAM-1 Activity

with Alternating P=S/P=O Linkages in a Uniform 2'-modified Oligomer

Isis #	Oligonucleotides Tested	
16952 (SEQ ID NO: 9)	**TCTGAGTAGCAGAGGAGCTC**	MOE, P=O
16953 (SEQ ID NO: 10)	GATCGCGTCGGACTATGAAG	**Scrambled Control[a]**
15537 (SEQ ID NO: 11)	TCTGAGTAGCAGAGGAGCTC	**MOE, P=S**
16954 (SEQ ID NO: 12)	GATCGCGTCGGACTATGAAG	**Scrambled Control**
18268 (SEQ ID NO: 13)	TCTGAGTAGCAGAGGAGCTC*	**MOE, P=S/P=O**

C=5-methyl -C in all sequences (except C*)

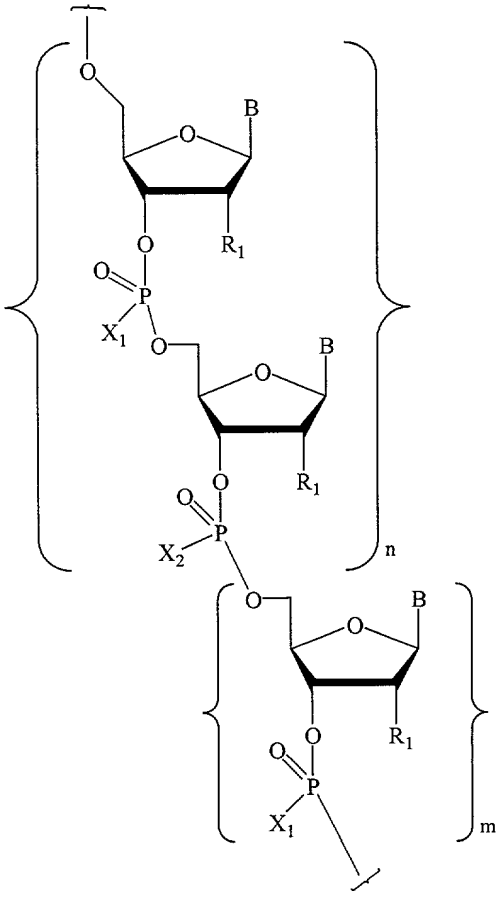
[a]same base composition

In the claims:

Please cancel claims 1-27 and 31-33.

Please rewrite claims 28-30 as follows.

28. (amended once) A method of treating an organism having a disease characterized by the undesired production of a protein, said method comprising contacting said organism with a compound of formula:



wherein:

each B is a nucleobase;

one of X_1 or X_2 is O, and the other of X_1 or X_2 is S;

each R_1, is, independently, H, hydroxyl, C_1-C_{20} alkyl, C_3-C_{20} alkenyl, C_2-C_{20} alkynyl, halogen, thiol, keto, carboxyl, nitro, nitroso, nitrile, trifluoromethyl, trifluoromethoxy, O-alkyl, S-alkyl, NH-alkyl, N-dialkyl, O-aryl, S-aryl, NH-aryl, O-aralkyl, S-aralkyl, NH-aralkyl, amino, N-phthalimido, imidazole, azido, hydrazino, hydroxylamino, isocyanato, sulfoxide, sulfone, sulfide, disulfide, silyl, aryl, heterocycle, carbocycle, intercalator, reporter molecule, conjugate, polyamine, polyamide, polyalkylene glycol, or polyether;

or R_1 is a group of formula $Z\text{-}R_{22}\text{-}(R_{23})_v$;

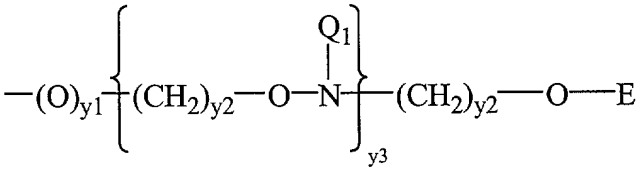
Z is O, S, NH, or $N\text{-}R_{22}\text{-}(R_{23})_v$;

R_{22} is C_1-C_{20} alkyl, C_2-C_{20} alkenyl, or C_2-C_{20} alkynyl;

R_{23} is hydrogen, amino, halogen, hydroxyl, thiol, keto, carboxyl, nitro, nitroso, nitrile, trifluoromethyl, trifluoromethoxy, O-alkyl, S-alkyl, NH-alkyl, N-dialkyl, O-aryl, S-aryl, NH-aryl, O-aralkyl, S-aralkyl, NH-aralkyl, amino, N-phthalimido, imidazole, azido, hydrazino, hydroxylamino, isocyanato, sulfoxide, sulfone, sulfide, disulfide, silyl, aryl, heterocycle, carbocycle, intercalator, reporter molecule, conjugate, polyamine, polyamide, polyalkylene glycol, polyether, a group that enhances the pharmacodynamic properties of oligonucleotides, or a group that enhances the pharmacokinetic properties of oligonucleotides;

v is from 0 to about 10;

or R_1 has the formula:



wherein:

y1 is 0 or 1;

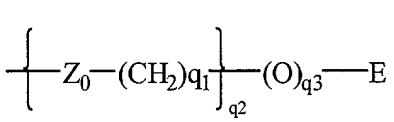
y2 is independently 0 to 10;

y3 is 1 to 10;

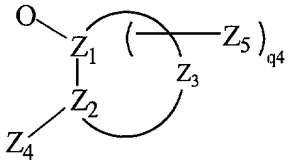
E is C_1-C_{10} alkyl, $N(Q_1)(Q_2)$ or $N=C(Q_1)(Q_2)$;

each Q_1 and Q_2 is, independently, H, C_1-C_{10} alkyl, substituted alkyl, dialkylaminoalkyl, a nitrogen protecting group, a tethered or untethered conjugate group, a linker to a solid support; or Q_1 and Q_2, together, are joined in a nitrogen protecting group or a ring structure that can include at least one additional heteroatom selected from N and O;

or R_1 has one of formula I or II:



I



II

wherein:

Z_0 is O, S, or NH;

q^1 is from 0 to 10;

q^2 is from 1 to 10;

q^3 is 0 or 1;

q^4 is, 0, 1 or 2;

Z_4 is OM_1, SM_1, or $N(M_1)_2$;

each M_1 is, independently, H, C_1-C_8 alkyl, C_1-C_8 haloalkyl, $C(=NH)N(H)M_2$, $C(=O)N(H)M_2$ or $OC(=O)N(H)M_2$;

M_2 is H or C_1-C_8 alkyl;

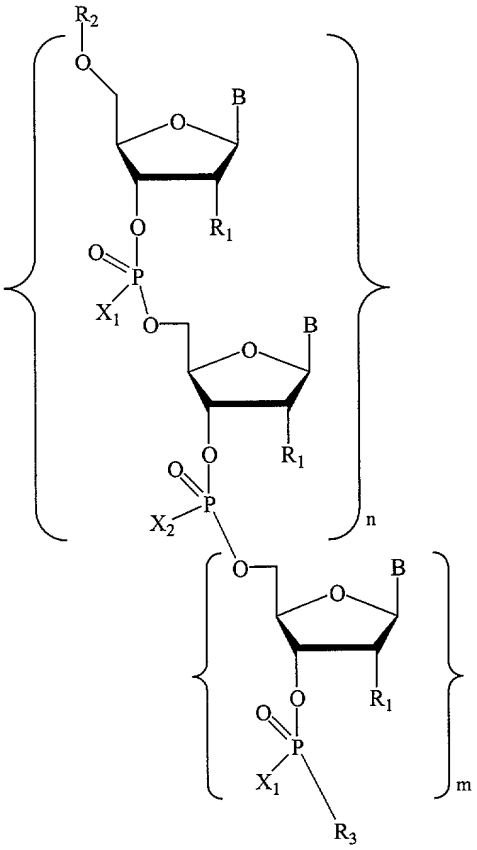
Z_1, Z_2 and Z_3 comprise a ring system having from about 4 to about 7 carbon atoms, or having from about 3 to about 6 carbon atoms and 1 or 2 hetero atoms wherein said hetero atoms are selected from oxygen, nitrogen and sulfur, and wherein said ring system is aliphatic, unsaturated aliphatic, aromatic, or saturated or unsaturated heterocyclic; and

Z_5 is alkyl or haloalkyl having 1 to about 10 carbon atoms, alkenyl having 2 to about 10 carbon atoms, alkynyl having 2 to about 10 carbon atoms, aryl having 6 to about 14 carbon atoms, $N(Q_1)(Q_2)$, OQ_1, halo, SQ_1 or CN;

n is from 2 to 50; and

m is 0 or 1.

29. (amended once) A method of treating an organism having a disease characterized by the undesired production of a protein, said method comprising contacting said organism with a compound of formula:



wherein:

each B is a nucleobase;

X_1 is S;

X_2 is O;

each R_1, is, independently, H, hydroxyl, C_1-C_{20} alkyl, C_3-C_{20} alkenyl, C_2-C_{20} alkynyl, halogen, thiol, keto, carboxyl, nitro, nitroso, nitrile, trifluoromethyl, trifluoromethoxy, O-alkyl, S-alkyl, NH-alkyl, N-dialkyl, O-aryl, S-aryl, NH-aryl, O-aralkyl, S-aralkyl, NH-aralkyl, amino, N-phthalimido, imidazole, azido, hydrazino, hydroxylamino, isocyanato, sulfoxide, sulfone, sulfide, disulfide, silyl, aryl, heterocycle, carbocycle, intercalator, reporter molecule, conjugate, polyamine, polyamide, polyalkylene glycol, or polyether;

or R_1 is a group of formula Z-R_{22}-$(R_{23})_v$;

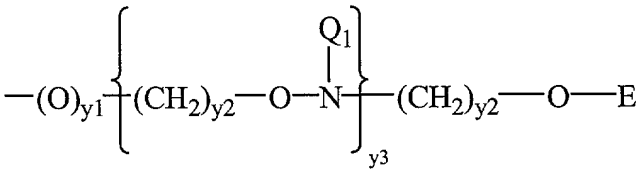
Z is O, S, NH, or N-R_{22}-$(R_{23})_v$;

R_{22} is C_1-C_{20} alkyl, C_2-C_{20} alkenyl, or C_2-C_{20} alkynyl;

R_{23} is hydrogen, amino, halogen, hydroxyl, thiol, keto, carboxyl, nitro, nitroso, nitrile, trifluoromethyl, trifluoromethoxy, O-alkyl, S-alkyl, NH-alkyl, N-dialkyl, O-aryl, S-aryl, NH-aryl, O-aralkyl, S-aralkyl, NH-aralkyl, amino, N-phthalimido, imidazole, azido, hydrazino, hydroxylamino, isocyanato, sulfoxide, sulfone, sulfide, disulfide, silyl, aryl, heterocycle, carbocycle, intercalator, reporter molecule, conjugate, polyamine, polyamide, polyalkylene glycol, polyether, a group that enhances the pharmacodynamic properties of oligonucleotides, or a group that enhances the pharmacokinetic properties of oligonucleotides;

v is from 0 to about 10;

or R_1 has the formula:



y1 is 0 or 1;

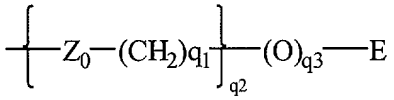
y2 is independently 0 to 10;

y3 is 1 to 10;

E is C_1-C_{10} alkyl, $N(Q_1)(Q_2)$ or $N=C(Q_1)(Q_2)$;

each Q_1 and Q_2 is, independently, H, C_1-C_{10} alkyl, substituted alkyl, dialkylaminoalkyl, a nitrogen protecting group, a tethered or untethered conjugate group, a linker to a solid support; or Q_1 and Q_2, together, are joined in a nitrogen protecting group or a ring structure that can include at least one additional heteroatom selected from N and O;

or R_1 has one of formula I or II:



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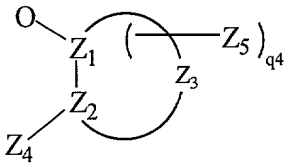


II

wherein:

Z_0 is O, S, or NH;

q^1 is from 0 to 10;

q^2 is from 1 to 10;

q^3 is 0 or 1;

q^4 is, 0, 1 or 2;

Z_4 is OM_1, SM_1, or $N(M_1)_2$;

each M_1 is, independently, H, C_1-C_8 alkyl, C_1-C_8 haloalkyl, $C(=NH)N(H)M_2$, $C(=O)N(H)M_2$ or $OC(=O)N(H)M_2$;

M_2 is H or C_1-C_8 alkyl;

Z_1, Z_2 and Z_3 comprise a ring system having from about 4 to about 7 carbon atoms, or having from about 3 to about 6 carbon atoms and 1 or 2 hetero atoms wherein said hetero atoms are selected from oxygen, nitrogen and sulfur, and wherein said ring system is aliphatic, unsaturated aliphatic, aromatic, or saturated or unsaturated heterocyclic; and

Z_5 is alkyl or haloalkyl having 1 to about 10 carbon atoms, alkenyl having 2 to

about 10 carbon atoms, alkynyl having 2 to about 10 carbon atoms, aryl having 6 to about 14 carbon atoms, $N(Q_1)(Q_2)$, OQ_1, halo, SQ_1 or CN;

n is from 2 to 50; and

m is 0 or 1;

R_2 is H, a hydroxyl protecting group, or an oligonucleotide; and

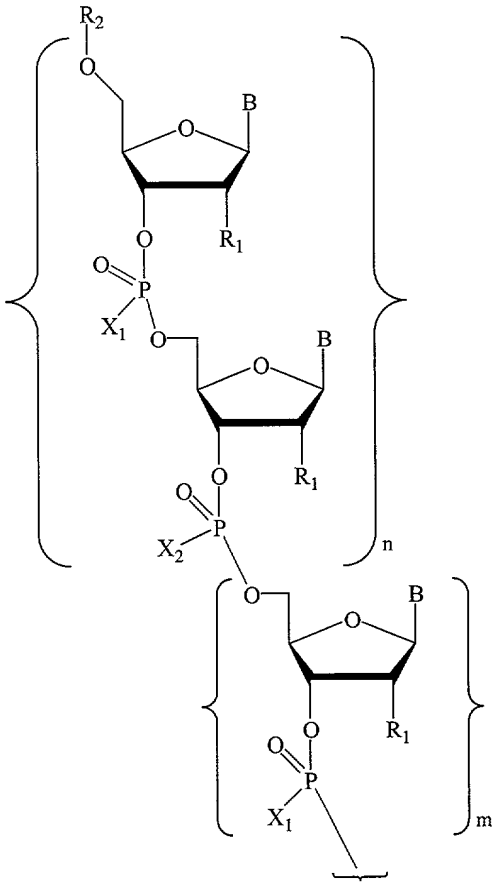
R_3 is OH, an oligonucleotide, or a linker connected to a solid support.

30. (amended once) A method of treating an organism having a disease characterized by the undesired production of a protein, said method comprising contacting said organism with a compound of formula:

(5') W^1-W^2-W^3 (3')

wherein:

W^1 has the Formula:



wherein:

each B is a nucleobase;

one of X_1 or X_2 is O, and the other of X_1 or X_2 is S;

each R_1, is, independently, H, hydroxyl, C_1-C_{20} alkyl, C_3-C_{20} alkenyl, C_2-C_{20} alkynyl, halogen, thiol, keto, carboxyl, nitro, nitroso, nitrile, trifluoromethyl, trifluoromethoxy, O-alkyl, S-alkyl, NH-alkyl, N-dialkyl, O-aryl, S-aryl, NH-aryl, O-aralkyl, S-aralkyl, NH-aralkyl, amino, N-phthalimido, imidazole, azido, hydrazino, hydroxylamino, isocyanato, sulfoxide, sulfone, sulfide, disulfide, silyl, aryl, heterocycle, carbocycle, intercalator, reporter molecule, conjugate, polyamine, polyamide, polyalkylene glycol, or polyether;

or R_1 is a group of formula Z-R_{22}-$(R_{23})_v$;

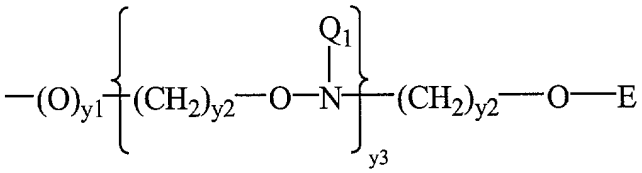
Z is O, S, NH, or N-R_{22}-$(R_{23})_v$;

R_{22} is C_1-C_{20} alkyl, C_2-C_{20} alkenyl, or C_2-C_{20} alkynyl;

R_{23} is hydrogen, amino, halogen, hydroxyl, thiol, keto, carboxyl, nitro, nitroso, nitrile, trifluoromethyl, trifluoromethoxy, O-alkyl, S-alkyl, NH-alkyl, N-dialkyl, O-aryl, S-aryl, NH-aryl, O-aralkyl, S-aralkyl, NH-aralkyl, amino, N-phthalimido, imidazole, azido, hydrazino, hydroxylamino, isocyanato, sulfoxide, sulfone, sulfide, disulfide, silyl, aryl, heterocycle, carbocycle, intercalator, reporter molecule, conjugate, polyamine, polyamide, poly-alkylene glycol, polyether, a group that enhances the pharmacodynamic properties of oligonucleotides, or a group that enhances the pharmacokinetic properties of oligonucleotides;

v is from 0 to about 10;

or R_1 has the formula:



y1 is 0 or 1;

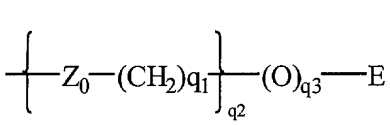
y2 is independently 0 to 10;

y3 is 1 to 10;

E is C_1-C_{10} alkyl, $N(Q_1)(Q_2)$ or $N=C(Q_1)(Q_2)$;

each Q_1 and Q_2 is, independently, H, C_1-C_{10} alkyl, substituted alkyl, dialkylaminoalkyl, a nitrogen protecting group, a tethered or untethered conjugate group, a linker to a solid support; or Q_1 and Q_2, together, are joined in a nitrogen protecting group or a ring structure that can include at least one additional heteroatom selected from N and O;

or R_1 has one of formula I or II:



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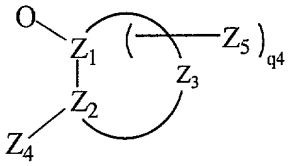


II

wherein:

Z_0 is O, S, or NH;

q^1 is from 0 to 10;

q^2 is from 1 to 10;

q^3 is 0 or 1;

q^4 is, 0, 1 or 2;

Z_4 is OM_1, SM_1, or $N(M_1)_2$;

each M_1 is, independently, H, C_1-C_8 alkyl, C_1-C_8 haloalkyl, $C(=NH)N(H)M_2$, $C(=O)N(H)M_2$ or $OC(=O)N(H)M_2$;

M_2 is H or C_1-C_8 alkyl;

Z_1, Z_2 and Z_3 comprise a ring system having from about 4 to about 7 carbon atoms, or having from about 3 to about 6 carbon atoms and 1 or 2 hetero atoms wherein said hetero atoms are selected from oxygen, nitrogen and sulfur, and wherein said ring system is aliphatic, unsaturated aliphatic, aromatic, or saturated or unsaturated heterocyclic; and

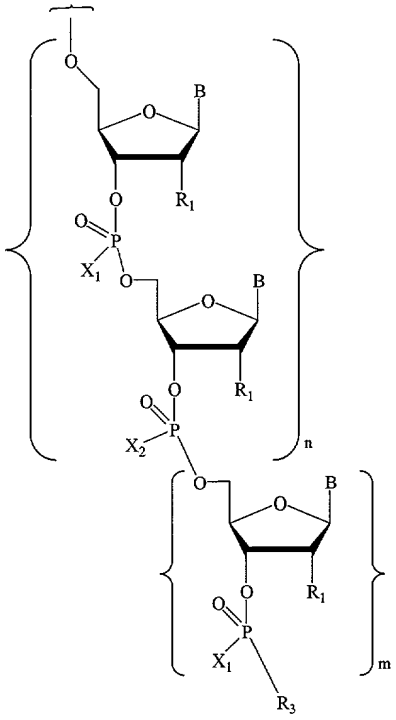
Z_5 is alkyl or haloalkyl having 1 to about 10 carbon atoms, alkenyl having 2 to about 10 carbon atoms, alkynyl having 2 to about 10 carbon atoms, aryl having 6 to about 14 carbon atoms, $N(Q_1)(Q_2)$, OQ_1, halo, SQ_1 or CN;

n is from 2 to 50; and

m is 0 or 1;

R_2 is H, a hydroxyl protecting group, or an oligonucleotide;

W^3 has the Formula:



wherein R_3 is OH, an oligonucleotide, or a linker connected to a solid support; and

W^2 is a plurality of covalently bound nucleosides linked by phosphodiester or phosphorothioate linkages.

Please add new claims 34-51 as follows.

--34. (new) The method of claim 28 wherein R_1 is -O-CH_2-CH_2-O-CH_3.

35. (new) The method of claim 28 wherein n is about 5 to about 50.

36. (new) The method of claim 28 wherein n is about 8 to about 30.

37. (new) The method of claim 28 wherein n is about 4 to about 15.

38. (new) The method of claim 28 wherein n is 2 to about 10.

39. (new) The method of claim 29 wherein R_1 is $-O-CH_2-CH_2-O-CH_3$.

40. (new) The method of claim 29 wherein R_2 is H, and R_3 is OH.

41. (new) The method of claim 29 wherein R_2 is a phosphodiester-linked oligonucleotide or a phosphorothioate linked oligonucleotide.

42. (new) The method of claim 29 wherein R_3 is a phosphodiester-linked oligonucleotide or a phosphorothioate linked oligonucleotide.

43. (new) The method of claim 29 R_2 and R_3 are each a phosphodiester-linked oligonucleotide or a phosphorothioate linked oligonucleotide.

44. (new) The method of claim 30 wherein R_1 is $-O-CH_2-CH_2-O-CH_3$.

45. (new) The method of claim 30 wherein R_2 is H, and R_3 is OH.

46. (new) The method of claim 30 wherein n is about 5 to about 50.

47. (new) The method of claim 30 wherein n is about 8 to about 30.

48. (new) The method of claim 30 wherein n is about 4 to about 15.

49. (new) The method of claim 30 wherein n is 2 to about 10.

50. (new) The method of claim 30 wherein W^2 is a plurality of covalently bound nucleosides linked by phosphodiester linkages.

51. (new) The method of claim 30 wherein W^2 is a plurality of covalently bound nucleosides linked by phosphorothioate linkages.--

REMARKS

Claims 28-30 and 34-51 are pending in this application.

Claims 1-27 and 31-33 have been canceled.

Claims 28-30 have been amended. Support for the amendments can be found, for example, in the original claims and throughout the specification. No new matter has been added.

Claims 34-51 have been added. Support for the added claims can be found, for example, in the original claims and throughout the specification. No new matter has been added.

Applicants believe that the claims presently before the Examiner patentably define the invention over the applied art and are otherwise in condition for ready allowance. An early Office Action to that effect is, therefore, earnestly solicited.

Attached hereto is a marked-up version of the changes made to the specification and claims by the current amendment. The attached page is captioned **"Version with markings to show changes made."**

Respectfully submitted,

Christine A. Goddard, Ph.D.
Registration No. 46,731

Date: September 27, 2001

WOODCOCK WASHBURN KURTZ
MACKIEWICZ & NORRIS LLP
One Liberty Place - 46th Floor
Philadelphia, PA 19103
(215) 568-3100

VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the specification:

The section on page 1 having the section heading **CROSS REFERENCE TO RELATED APPLICATIONS** has been amended as follows.

This application is a continuation of U.S. Ser. No. 09/349,007, filed July 7, 1999, which in turn is a continuation-in-part of U.S. Ser. No. 09/115,025, filed July 14, 1998, the disclosures of each of which are incorporated herein by reference in their entireties [the content of which is incorporated herein by reference in its entirety].

Table I on page 50 has been amended as follows.

Table I
Oligonucleotides containing Staggered PS/PO linkages

Oligo #	ISIS #	Sequence (5'-3')[1]	Backbone	Chemistry	Target
1	18268 staggered oligomer	5'-T_S**$C^m{}_O T_S G_O A_S G_O T_S A_O G_S C^m{}_O A_S G_O A_S G_O G_S A_O G_S C^m{}_O T_S$**C-3' SEQ ID NO: 1	P=S/P=O	2'-*O*-MOE	*Human ICAM -1*
2	22592 staggered gapmer	5'-**$A_S T_O G_S C^m{}_O A_S T_O$** $T_S C_S{}^m T_S G_S C_S{}^m C_S{}^m C_S{}^m C^m{}_O$ **$C^m{}_S A_O A_S G_O G_S A$**-3' SEQ ID NO: 2	P=S/P=O	2'-*O*-MOE & 2'-H	*mouse C-raf*
3	25303 staggered hemimer	5'-$G_S C^m{}_S C^m{}_S C^m{}_S A_S A_S G_S C^m{}_S T_S G_S G_S C^m{}_O$ **$A_S T_O C^m{}_S C^m{}_O G_S T_O C^m{}_S A$**-3' SEQ ID NO: 3	P=S/P=O	2'-*O*-MOE & 2'-H	*Human ICAM-1*

[1] All nucleosides in bold are 2'-*O* -MOE (2'-O-CH_2-CH_2-O-CH_3)

Table III on page 51 has been amended as follows.

Table III
Tm Values of Human ICAM-1 Antisense Oligonucleotide
ISIS 3067 and Analogs Against RNA Target

5'-TCT GAG TAG CAG AGG AGC TC-3' (SEQ ID NO:4)		
Oligonucleotide	**Modifications**	**Tm**
ISIS 3067 (SEQ ID NO: 5)	**P=S, 2'-deoxy DNA**	**50.1**
ISIS 11910 (SEQ ID NO: 4)	**P=O, 2'-deoxy DNA**	**58.4**
ISIS 11159 (SEQ ID NO: 6)	**P=S, 2'-MOE**	**79.2**
ISIS 11158 (SEQ ID NO: 7)	**P=O, 2'-MOE**	**86.6**
ISIS 18268 (SEQ ID NO: 8)	**P=O/P=S, STAGGERED 2'-MOE**	**84.0**

Table IV on page 53 has been amended as follows.

Table IV
Controlling P=S Linkages: ICAM-1 Activity
with Alternating P=S/P=O Linkages in a Uniform 2'-modified Oligomer

Isis #	Oligonucleotides Tested	
16952 (SEQ ID NO: 9)	**TCTGAGTAGCAGAGGAGCTC**	MOE, P=O
16953 (SEQ ID NO: 10)	GATCGCGTCGGACTATGAAG	**Scrambled Control[a]**
15537 (SEQ ID NO: 11)	TCTGAGTAGCAGAGGAGCTC	**MOE, P=S**
16954 (SEQ ID NO: 12)	GATCGCGTCGGACTATGAAG	**Scrambled Control**
18268 (SEQ ID NO: 13)	TCTGAGTAGCAGAGGAGCTC*	**MOE, P=S/P=O**

C=5-methyl -C in all sequences (except C*)

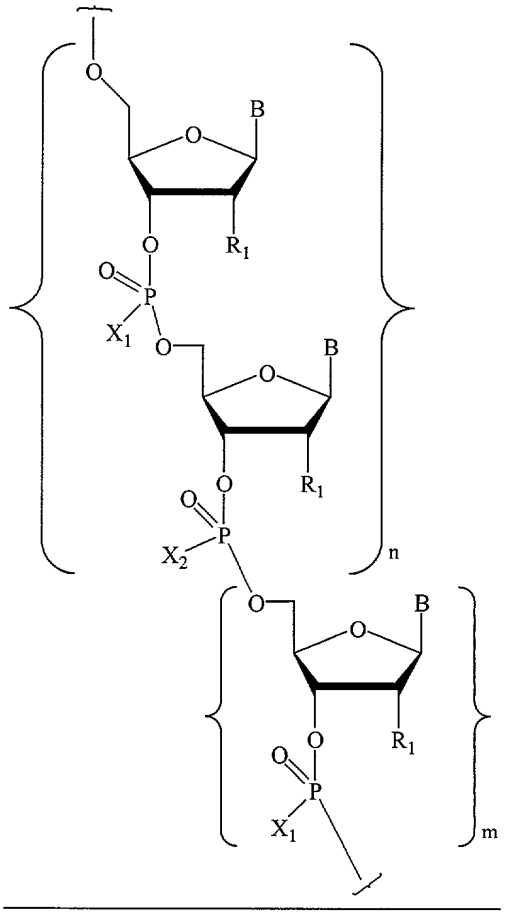
[a]same base composition

In the claims:

Claims 34-51 have been added.

Claims 28-30 have been rewritten as follows.

28. (amended once) A method of treating an organism having a disease characterized by the undesired production of a protein, said method comprising contacting said organism with a compound of [claim 1.] formula:



wherein:

each B is a nucleobase;

one of X_1 or X_2 is O, and the other of X_1 or X_2 is S;

each R_1, is, independently, H, hydroxyl, C_1-C_{20} alkyl, C_3-C_{20} alkenyl, C_2-C_{20} alkynyl, halogen, thiol, keto, carboxyl, nitro, nitroso, nitrile, trifluoromethyl, trifluoromethoxy, O-alkyl, S-alkyl, NH-alkyl, N-dialkyl, O-aryl, S-aryl, NH-aryl, O-aralkyl, S-aralkyl, NH-aralkyl, amino, N-phthalimido, imidazole, azido, hydrazino, hydroxylamino, isocyanato, sulfoxide, sulfone, sulfide, disulfide, silyl, aryl, heterocycle, carbocycle, intercalator, reporter molecule, conjugate, polyamine, polyamide, polyalkylene glycol, or polyether;

or R_1 is a group of formula $Z\text{-}R_{22}\text{-}(R_{23})_{v2}$;

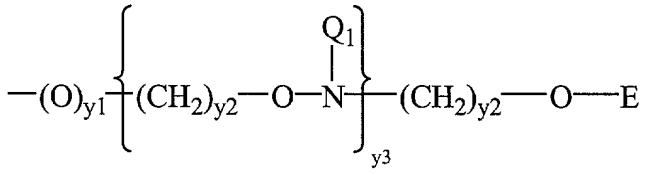
Z is O, S, NH, or $N\text{-}R_{22}\text{-}(R_{23})_{v2}$;

R_{22} is C_1-C_{20} alkyl, C_2-C_{20} alkenyl, or C_2-C_{20} alkynyl;

R_{23} is hydrogen, amino, halogen, hydroxyl, thiol, keto, carboxyl, nitro, nitroso, nitrile, trifluoromethyl, trifluoromethoxy, O-alkyl, S-alkyl, NH-alkyl, N-dialkyl, O-aryl, S-aryl, NH-aryl, O-aralkyl, S-aralkyl, NH-aralkyl, amino, N-phthalimido, imidazole, azido, hydrazino, hydroxylamino, isocyanato, sulfoxide, sulfone, sulfide, disulfide, silyl, aryl, heterocycle, carbocycle, intercalator, reporter molecule, conjugate, polyamine, polyamide, polyalkylene glycol, polyether, a group that enhances the pharmacodynamic properties of oligonucleotides, or a group that enhances the pharmacokinetic properties of oligonucleotides;

v is from 0 to about 10;

or R_1 has the formula:



wherein:

y1 is 0 or 1;

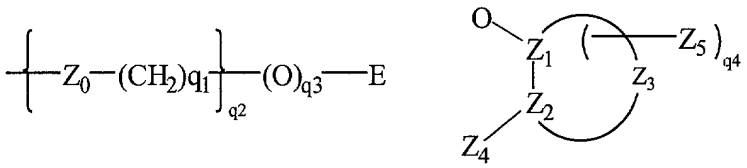
y2 is independently 0 to 10;

y3 is 1 to 10;

E is C_1-C_{10} alkyl, $N(Q_1)(Q_2)$ or $N=C(Q_1)(Q_2)$;

each Q_1 and Q_2 is, independently, H, C_1-C_{10} alkyl, substituted alkyl, dialkylaminoalkyl, a nitrogen protecting group, a tethered or untethered conjugate group, a linker to a solid support; or Q_1 and Q_2, together, are joined in a nitrogen protecting group or a ring structure that can include at least one additional heteroatom selected from N and O;

or R_1 has one of formula I or II:



I II

wherein:

Z_0 is O, S, or NH;

q^1 is from 0 to 10;

q^2 is from 1 to 10;

q^3 is 0 or 1;

q^4 is, 0, 1 or 2;

Z_4 is OM_1, SM_1, or $N(M_1)_2$;

each M_1 is, independently, H, C_1-C_8 alkyl, C_1-C_8 haloalkyl, $C(=NH)N(H)M_2$, $C(=O)N(H)M_2$ or $OC(=O)N(H)M_2$;

M_2 is H or C_1-C_8 alkyl;

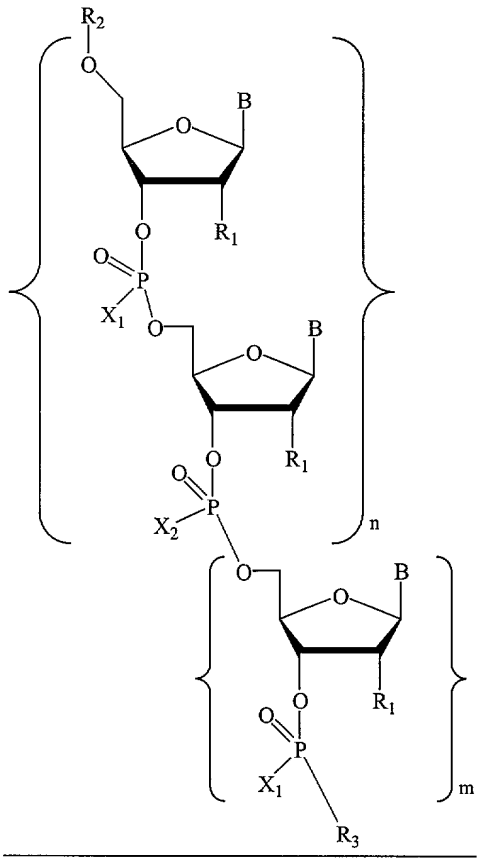
Z_1, Z_2 and Z_3 comprise a ring system having from about 4 to about 7 carbon atoms, or having from about 3 to about 6 carbon atoms and 1 or 2 hetero atoms wherein said hetero atoms are selected from oxygen, nitrogen and sulfur, and wherein said ring system is aliphatic, unsaturated aliphatic, aromatic, or saturated or unsaturated heterocyclic; and

Z_5 is alkyl or haloalkyl having 1 to about 10 carbon atoms, alkenyl having 2 to about 10 carbon atoms, alkynyl having 2 to about 10 carbon atoms, aryl having 6 to about 14 carbon atoms, $N(Q_1)(Q_2)$, OQ_1, halo, SQ_1 or CN;

n is from 2 to 50; and

m is 0 or 1.

29. (amended once) A method of treating an organism having a disease characterized by the undesired production of a protein, said method comprising contacting said organism with a compound of [claim 7.] formula:



wherein:

each B is a nucleobase;

X_1 is S;

X_2 is O;

each R_1, is, independently, H, hydroxyl, C_1-C_{20} alkyl, C_3-C_{20} alkenyl, C_2-C_{20} alkynyl, halogen, thiol, keto, carboxyl, nitro, nitroso, nitrile, trifluoromethyl, trifluoromethoxy, O-alkyl, S-alkyl, NH-alkyl, N-dialkyl, O-aryl, S-aryl, NH-aryl, O-aralkyl, S-aralkyl, NH-aralkyl, amino, N-phthalimido, imidazole, azido, hydrazino, hydroxylamino, isocyanato, sulfoxide, sulfone, sulfide, disulfide, silyl, aryl, heterocycle, carbocycle, intercalator, reporter molecule, conjugate, polyamine, polyamide, polyalkylene glycol, or polyether;

or R_1 is a group of formula Z-R_{22}-$(R_{23})_{v2}$;

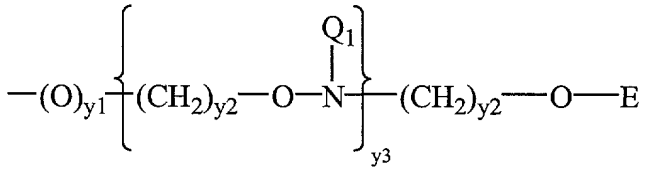
Z is O, S, NH, or N-R_{22}-$(R_{23})_{v2}$;

R_{22} is C_1-C_{20} alkyl, C_2-C_{20} alkenyl, or C_2-C_{20} alkynyl;

R_{23} is hydrogen, amino, halogen, hydroxyl, thiol, keto, carboxyl, nitro, nitroso, nitrile, trifluoromethyl, trifluoromethoxy, O-alkyl, S-alkyl, NH-alkyl, N-dialkyl, O-aryl, S-aryl, NH-aryl, O-aralkyl, S-aralkyl, NH-aralkyl, amino, N-phthalimido, imidazole, azido, hydrazino, hydroxylamino, isocyanato, sulfoxide, sulfone, sulfide, disulfide, silyl, aryl, heterocycle, carbocycle, intercalator, reporter molecule, conjugate, polyamine, polyamide, polyalkylene glycol, polyether, a group that enhances the pharmacodynamic properties of oligonucleotides, or a group that enhances the pharmacokinetic properties of oligonucleotides;

v is from 0 to about 10;

or R_1 has the formula:



y1 is 0 or 1;

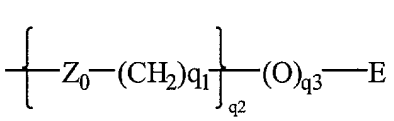
y2 is independently 0 to 10;

y3 is 1 to 10;

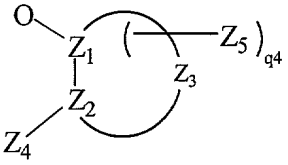
E is C_1-C_{10} alkyl, $N(Q_1)(Q_2)$ or $N=C(Q_1)(Q_2)$;

each Q_1 and Q_2 is, independently, H, C_1-C_{10} alkyl, substituted alkyl, dialkylaminoalkyl, a nitrogen protecting group, a tethered or untethered conjugate group, a linker to a solid support; or Q_1 and Q_2, together, are joined in a nitrogen protecting group or a ring structure that can include at least one additional heteroatom selected from N and O;

or R_1 has one of formula I or II:



I



II

wherein:

Z_0 is O, S, or NH;

q^1 is from 0 to 10;

q^2 is from 1 to 10;

q^3 is 0 or 1;

q^4 is, 0, 1 or 2;

Z_4 is OM_1, SM_1, or $N(M_1)_2$;

each M_1 is, independently, H, C_1-C_8 alkyl, C_1-C_8 haloalkyl, $C(=NH)N(H)M_2$, $C(=O)N(H)M_2$ or $OC(=O)N(H)M_2$;

M_2 is H or C_1-C_8 alkyl;

Z_1, Z_2 and Z_3 comprise a ring system having from about 4 to about 7 carbon atoms, or having from about 3 to about 6 carbon atoms and 1 or 2 hetero atoms wherein said hetero atoms are selected from oxygen, nitrogen and sulfur, and wherein said ring system is aliphatic, unsaturated aliphatic, aromatic, or saturated or unsaturated heterocyclic; and

Z_5 is alkyl or haloalkyl having 1 to about 10 carbon atoms, alkenyl having 2 to about 10 carbon atoms, alkynyl having 2 to about 10 carbon atoms, aryl having 6 to about 14 carbon atoms, $N(Q_1)(Q_2)$, OQ_1, halo, SQ_1 or CN;

n is from 2 to 50; and

m is 0 or 1;

R_2 is H, a hydroxyl protecting group, or an oligonucleotide; and

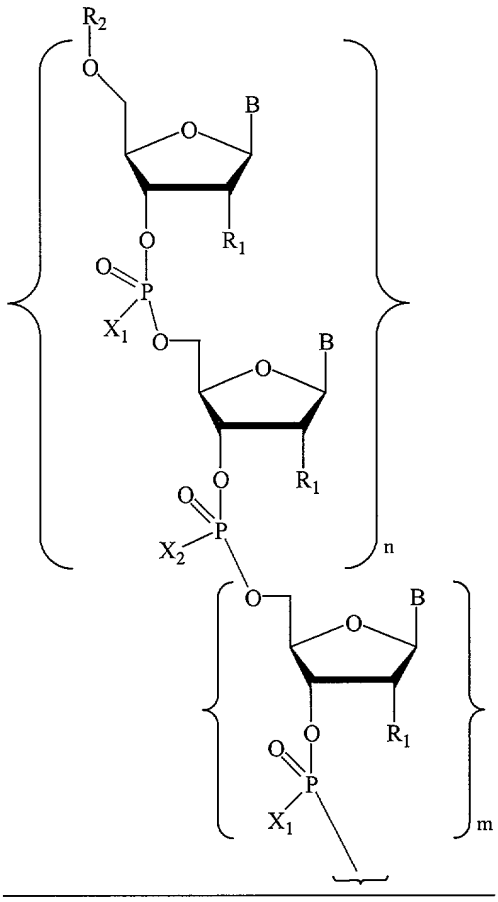
R_3 is OH, an oligonucleotide, or a linker connected to a solid support.

30. (amended once) A method of treating an organism having a disease characterized by the undesired production of a protein, said method comprising contacting said organism with a compound of [claim 13.] formula:

(5') W^1-W^2-W^3 (3')

wherein:

W^1 has the Formula:



wherein:

each B is a nucleobase;

one of X_1 or X_2 is O, and the other of X_1 or X_2 is S;

each R_1, is, independently, H, hydroxyl, C_1-C_{20} alkyl, C_3-C_{20} alkenyl, C_2-C_{20} alkynyl, halogen, thiol, keto, carboxyl, nitro, nitroso, nitrile, trifluoromethyl, trifluoromethoxy, O-alkyl, S-alkyl, NH-alkyl, N-dialkyl, O-aryl, S-aryl, NH-aryl, O-aralkyl, S-aralkyl, NH-aralkyl, amino, N-phthalimido, imidazole, azido, hydrazino, hydroxylamino, isocyanato, sulfoxide, sulfone, sulfide, disulfide, silyl, aryl, heterocycle, carbocycle, intercalator, reporter molecule, conjugate, polyamine, polyamide, polyalkylene glycol, or polyether;

or R_1 is a group of formula Z-R_{22}-$(R_{23})_v$;

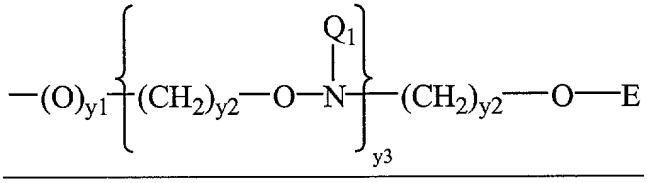
Z is O, S, NH, or N-R_{22}-(R_{23})$_v$;

R_{22} is C_1-C_{20} alkyl, C_2-C_{20} alkenyl, or C_2-C_{20} alkynyl;

R_{23} is hydrogen, amino, halogen, hydroxyl, thiol, keto, carboxyl, nitro, nitroso, nitrile, trifluoromethyl, trifluoromethoxy, O-alkyl, S-alkyl, NH-alkyl, N-dialkyl, O-aryl, S-aryl, NH-aryl, O-aralkyl, S-aralkyl, NH-aralkyl, amino, N-phthalimido, imidazole, azido, hydrazino, hydroxylamino, isocyanato, sulfoxide, sulfone, sulfide, disulfide, silyl, aryl, heterocycle, carbocycle, intercalator, reporter molecule, conjugate, polyamine, polyamide, poly-alkylene glycol, polyether, a group that enhances the pharmacodynamic properties of oligonucleotides, or a group that enhances the pharmacokinetic properties of oligonucleotides;

v is from 0 to about 10;

or R_1 has the formula:



y1 is 0 or 1;

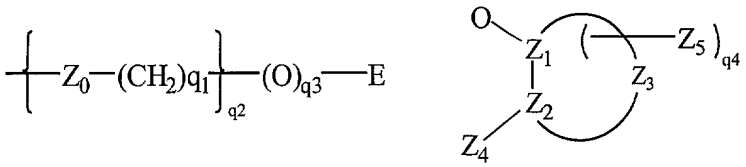
y2 is independently 0 to 10;

y3 is 1 to 10;

E is C_1-C_{10} alkyl, N(Q_1)(Q_2) or N=C(Q_1)(Q_2);

each Q_1 and Q_2 is, independently, H, C_1-C_{10} alkyl, substituted alkyl, dialkylaminoalkyl, a nitrogen protecting group, a tethered or untethered conjugate group, a linker to a solid support; or Q_1 and Q_2, together, are joined in a nitrogen protecting group or a ring structure that can include at least one additional heteroatom selected from N and O;

or R_1 has one of formula I or II:



I II

wherein:

Z_0 is O, S, or NH;

q^1 is from 0 to 10;

q^2 is from 1 to 10;

q^3 is 0 or 1;

q^4 is, 0, 1 or 2;

Z_4 is OM_1, SM_1, or $N(M_1)_2$;

each M_1 is, independently, H, C_1-C_8 alkyl, C_1-C_8 haloalkyl, $C(=NH)N(H)M_2$, $C(=O)N(H)M_2$ or $OC(=O)N(H)M_2$;

M_2 is H or C_1-C_8 alkyl;

Z_1, Z_2 and Z_3 comprise a ring system having from about 4 to about 7 carbon atoms, or having from about 3 to about 6 carbon atoms and 1 or 2 hetero atoms wherein said hetero atoms are selected from oxygen, nitrogen and sulfur, and wherein said ring system is aliphatic, unsaturated aliphatic, aromatic, or saturated or unsaturated heterocyclic; and

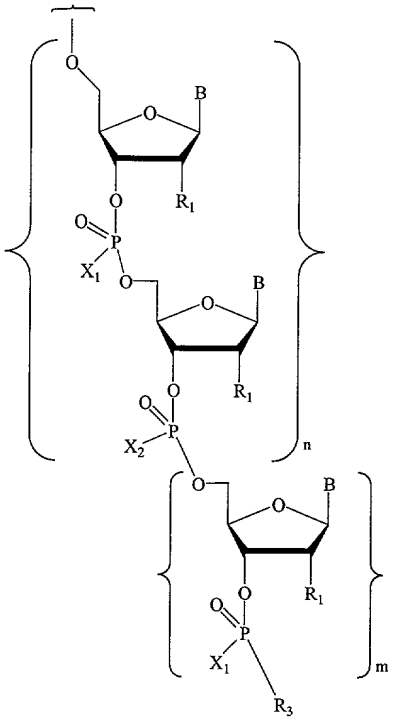
Z_5 is alkyl or haloalkyl having 1 to about 10 carbon atoms, alkenyl having 2 to about 10 carbon atoms, alkynyl having 2 to about 10 carbon atoms, aryl having 6 to about 14 carbon atoms, $N(Q_1)(Q_2)$, OQ_1, halo, SQ_1 or CN;

n is from 2 to 50; and

m is 0 or 1;

R_2 is H, a hydroxyl protecting group, or an oligonucleotide;

W^3 has the Formula:



wherein R_3 is OH, an oligonucleotide, or a linker connected to a solid support; and

W^2 is a plurality of covalently bound nucleosides linked by phosphodiester or phosphorothioate linkages.